ENQUIRY: JAPANESE REGULATIONS ON ORPHAN DRUGS

1. We spoke to the Research & Development Promotion Division of the Pharmaceutical Bureau, Ministry of Health & Welfare (MHW). It was no surprise to learn that Japan's regulations are modelled closely on the US Orphan Drug Act of 1983. In 1993, MHW implemented Japan's Orphan Drug Development System by revising Article 77 of the Pharmaceutical Affairs Law. Both orphan drugs and devices are covered. However, there are a few subtle differences in the way that the Japanese government supports companies developing orphan drugs.

2. To be designated as an orphan drug, a compound must meet the following three conditions:

- it must be a treatment for a rare disease, which effects less than 50,000 patients in Japan;

- there must be a clear demand for the compound, with no conventional medicine available; and

- successful development of the compound must be possible.

3. Companies apply to MHW for their compound to be designated as an orphan drug. MHW then ask one of the panels of the Central Pharmaceutical Affairs Council (CPAC) to examine the application. If approved, the Organisation for Adverse Drug Reaction Research (OADR) steps in. OADR is a QUANGO which administers industrial research projects for MHW. It also provides capital to establish R&D-oriented company per year. For approved orphan drugs, OADR provides the following incentives to companies:

- A grant to cover up to 50% of R&D costs.
- Guidance and advice on the new drug approval process.
- A tax deduction of 6% of R&D costs (excluding the amount of grant received). This tax deduction is limited to 10% of corporation tax.
- A "fast track", providing the highest priority in the new drug approval examination process.
- If needed, an extension of the allowable period for re-examination (the maximum is otherwise ten years).

4. As of April 1995, 80 drugs and four medical devices have been designated under this procedure. We have a complete list, in Japanese. I enclose a copy of an English language leaflet from OADR (*System for Promotion of Orphan Drug Development*, nine pages), which lists 46 drugs and two medical devices.

Comments

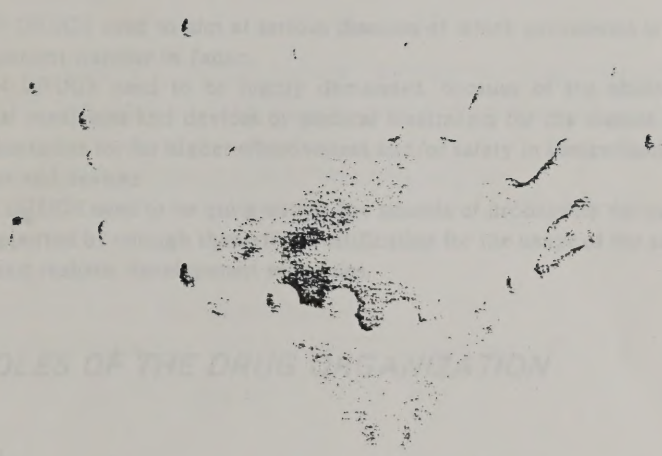
5. A close reading of this list reveals that most of Japan's orphan drugs have been developed by foreign companies.

6. We have reported on OADR in recent Embassy reports. Peter McDonald has copies. Our next report (which we hope to finish by the end of September) will have details of DNAVEC. This is a company set up with capital from OADR and six drug companies. It will provide the research infrastructure to try to establish a viable gene therapy industry in Japan. DNAVEC hope to develop generic vector technologies with widespread applications in the drug industry. However, they will also develop specialist gene therapies for hereditary diseases common in Japan). These are likely to be classified as orphan drugs.

British Embassy, Tokyo.

9 September 1996.

SYSTEMS FOR PROMOTION OF ORPHAN DRUG DEVELOPMENT



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The Organization for Drug ADR Relief,
R&D Promotion and Product Review
(abbr. The Drug Organization)

SYSTEMS FOR PROMOTION OF ORPHAN DRUG DEVELOPMENT

In spite of the urgent needs for medicines and medical devices for the treatment of aplastic anemia, AIDS and others, it is considered to be difficult to carry out adequate R&D efforts by private companies alone because of the limited number of the patients involved. To modify the status quo, partial amendments of both the Pharmaceutical Affairs Law and the Law Concerning the Drug Fund for ADR Relief and R&D Promotion and Product Review Promotion ware recently made. The Drug Organization (The Organization for Drug ADR Relief, R&D Promotion and Product Review) has provided and support program to the R&D of these medicines and medical devices (ORPHAN DRUGS) by private companies via close collaboration between government and industries, based on the amendments.

WHAT ARE ORPHAN DRUGS?

The requirements to be designated as ORPHAN DRUGS by The Ministry of Health and Welfare (MHW) are as follows:

1) ORPHAN DRUGS need to aim at serious diseases of which prevalence is less than 50,000 in total patient number in Japan.
2) ORPHAN DRUGS need to be highly demanded, because of the absence of either substitutional medicines and devices or medical treatments for the disease or because of the great expectation for far higher effectiveness and/or safety in comparison with the existing medicines and devices.
3) ORPHAN DRUGS need to be quite within the bounds of probability for successful development, supported by enough theoretical justification for the usage of the said medicines and devices and realistic development schedules.

THE ROLES OF THE DRUG ORGANIZATION

1. Granting

The Drug Organization makes grants to be used for the R&D of the said medicines and devices to private companies that have been disignated by the MHW as manufacturers or importers of ORPHAN DRUGS. The R&D cost subject to the granting is the direct one for the R&D and the amounts of grants are limited to one half of the cost. At the time of application for subsidies, each private company is required to submit an outline of R&D, cost, schedules for the R&D activities and other information. The Drug Organization makes grants after surveying these data (see tables on pages from 4 to 8 which show the orphan drugs to be granted in 1995). The manufacturers or importers of ORPHAN DRUGS to whom the grants are given will pay a part of their proceeds or profits (if exceed 100 million yen) after ORPHAN DRUGS are launched into the market (the total amount of payment is limited to that of the grant).

2. Guidance and Advice

In order to accelerate R&D of medicines and devices designated ORPHAN DRUGS, the Drug Organization provides guidance and advice for both of the R&D procedures of ORPHAN DRUGS and the preparation of New Drug Approval (NDA) in cooperation with the MHW.

3. Authorization for Tax Deduction

Based on the Special Taxation Measures Law, the Drug Organization authorizes the development costs of ORPHAN DRUGS that will be required for the period subjected to the grant, responding to the application from each company. Once authorized, six percent of their ORPHAN DRUGS R&D costs exclusive of the amount of grants given by the Drug Organization is deducted from their tax. The tax deduction is limited to 10% of the corporation tax or the income tax for the term.

ADDITIONAL PREFERENTIAL MEASURES FOR ORPHAN DRUGS

In addition to the supports for development promotion by the Drug Organization, ORPHAN DRUGS can receive following preferential measures from the MHW.

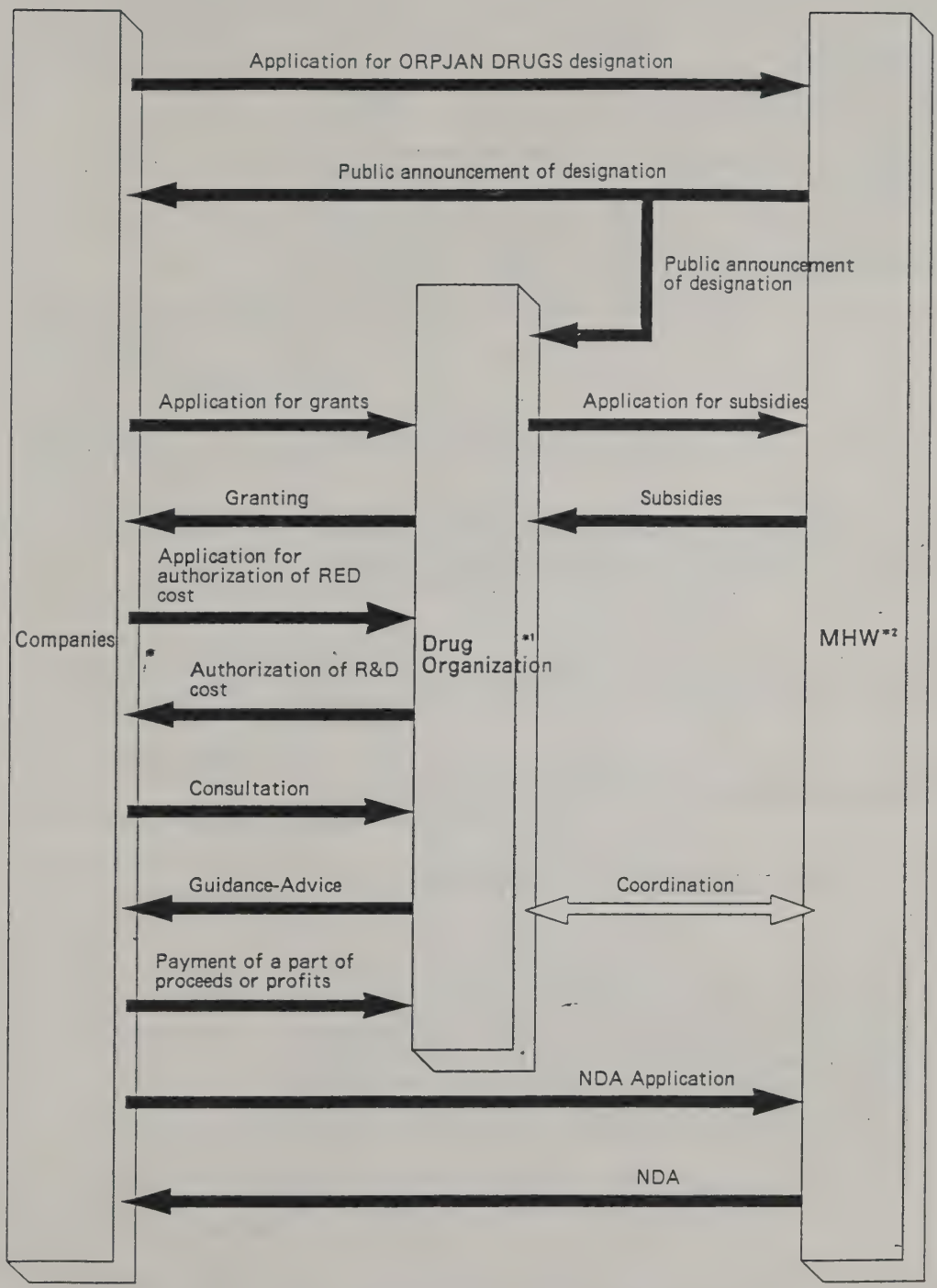
1. Priority in the Examination for New Drug Approvals

ORPHAN DRUGS are given the highest priority in the examination for New Drug Approvals.

2. Extension of the Term for Re-examination

The terms for re-examination of ORPHAN DRUGS are extended to the maximum of 10 years, compared with 6 years of ordinary new drugs.

Systems for Promotion of Orphan Drug Development



• 1 The Organization for Drug ADR Relief, R&D Promotion and Product Review

• 2 The Ministry of Health and Welfare

The orphan drugs designated in 1993

No.	Name〔Name of Manufacturer〕	Expected indications or effects
1	Mixture of L-arginine and L-arginine HCl (granule) and L-arginine HCl (injectable) 〔Roussel Morishita Co., Ltd.〕	The granule is used to improve the neurotic symptoms (vomiting, drowsiness, abnormal electroencephalogram and others) caused by hyperammonemia and the symptoms (growth and developmental disorder and others) caused by Arginine deficiency in the following diseases ; congenital abnormalities in urea cycle enzymes (deficiency of carbamoylphosphate synthetase, deficiency of ornithine transcarbamoylase, deficiency in argininosuccinic acid synthetase (citrullinemia) and deficiency of argininosuccinic acid lyase (arginino-succinicaciduria) and congenital abnormalities in amino acid transfer. The injectable is used to lower the blood ammonia levels abruptly in cases where the granule cannot control its sudden rise caused by exhaustion and others.
2	Horse anti-human thymocyte immunoglobulin 〔Upjohn Pharmaceuticals Limited〕	Aplastic anemia
3	Halofantrine HCl 〔SmithKline Beecham Seiyaku K.K.〕	Malaria
4	Dried and concentrated, activated human protein C 〔The Chemo-Sero-Therapeutic Research Institute, Teijin Limited〕	Improvement of the following diseases caused by congenital protein C deficiency, superficial and profound phlebothrombosis, pulmonary thromboembolism and purpura fulminans
5	Concentrated blood coagulation factor XIII derived from plasma 〔Hoechst Japan Limited〕	Suppression of development of intracranial hemorrhages in neonates
6	Sotalol 〔Bristol-Myers Squibb K.K.〕	Life-threatening ventricular tachycardiac arrhythmia (ventriculra tachycardia and fibrillation)
7	Tacrolimus 〔Fujisawa Pharmaceutical Co., Ltd.〕	Refractory uveitis, mainly observed in Behcet's disease
8	Piracetam 〔Taiho Pharmaceutical Co., Ltd., UCB Japan Co., Ltd.〕	Progressive myoclonus epilepsy (including lipidosis, Unverricht-Lundborg syndrome, Ramsay-Hunt syndrome, Lafora's disease, mitochondrial encephalomyopathy, neural ceroid lipofuscinosis), myoclonus following anoxic encephalipathy (Lance-Adams' syndrome), essential myoclonus, myoclonus complicated in Huntington's chorea, myoclonus complicated in Alzheimer's disease, drug-induced-myoclonus and other types of myoclonus of unknown etiology
9	L-1-methyl-4,5-dihydroorotyl-L-histidyl-L-proline amide 〔Tanabe Seiyaku Co., Ltd.〕	Spino-cerebrallar degeneration
10	Rilzol 〔Rhône-Poulenc Rorer Japan, Inc.〕	Amyotrophic lateral sclerosis

The orphan drugs designated in 1994

No.	Name(Name of Manufacturer)	Expected indications or effects
1	Ethyl icosapentate (Mochida Pharmaceutical Co., Ltd.)	Behcet's disease
2	Indium 111 (^{111}In) pentetreotide (Mallinckrodt Medical Co., Ltd.)	Diagnosis of gastrointestinal hormone producing tumors by scintigraphy
3	Interferon alfa (Sumitomo Pharmaceuticals Co., Ltd.)	Prolongation of survival time in patients with subacute sclerosing panencephalit is in combination with inosine pranobex
4	Interferon beta (Mochida Pharmaceutical Co., Ltd.)	Prolongation of survival time in patients with subacute sclerosing panencephalit is in combination with inosine pranobex
5	Interferon beta-1b (genetical recombination) (Nihon Schering K.K.)	Multiple sclerosis
6	Anti-human thymocyte rabbit immunoglobuline (Rhône-Poulenc Japan, Ltd.)	Treatment of graft versus host disease (GVHD) after bone marrow transplantation
7	Ursodesoxycholic acid (Tokyo Tanabe Co., Ltd.)	Primary biliary cirrhosis
8	Epoprostenol sodium (Nippon Wellcome K.K.)	Primary pulmonary hypertension
9	Mefloquine hydrochloride (SS Pharmaceutical Co., Ltd., Dojin Pharmaceutical Products Incorporated)	Treatment of malaria
10	Mefloquine hydrochloride (Nippon Roche K.K.)	Treatment of malaria
11	Octafluoropropane (Santen Pharmaceutical Co., Ltd.)	Intraocular gas tamponade or the treatment of idiopathic macular holes
12	Activated factor VII (genetical recombination) (Novo Nordisk Pharma Ltd.)	Treatment of bleeds in blood coagulation factor VIII deficiency (haemophilia A) or factor IX deficiency (haemophilia B) patients with inhibitors
13	Freeze-dried, activated human blood coagulation factor VII concentrate (The Chemo-Sero-Therapeutic Research Institute)	Treatment of bleeds in blood coagulation factor VIII deficiency (haemophilia A) or factor IX deficiency (haemophilia B) patients with inhibitors
14	BCG (Rhône-Poulenc Japan Ltd.)	Superficial bladder cancer, CIS (carcinoma in situ) of urinary bladder

No.	Name〔Name of Manufacturer〕	Expected indications or effects
15	Freeze-dried polyethylene glycol treated human normal inmmunoglobulin 〔Nihon Pharmaceutical Co., Ltd.〕	Chronic inflammatory demyelinating polyneuropathy
16	Clarithromycin 〔Taisho Pharmaceutical Co., Ltd., Dainabot Co., Ltd.〕	Disseminated mycobacterial infection in AIDS patients
17	Somatropin (genetical recombination) 〔Novo Nordisk Pharma Ltd.〕	Short stature without closure of epiphyseal line due to the follwing diseases chronic renal failure and achondroplasia
18	Somatropin (genetical recombination) 〔Sumitomo Pharmaceuticals Co., Ltd.〕	Short stature due to chronic renal insufficiency without closed epiphyses
19	Tiopronin 〔Santen Pharmaceutical Co., Ltd.〕	Cystinuria (include cystine calculus)
20	Transforming growth factor-beta 2 〔Santen Pharmaceutical Co., Ltd.〕	Treatment of idiopathic macular holes
21	Phenylalanine reduced milk (enzymatically degraded milk protein derived low-phenylalanine peptide powder mix) 〔Snow Brand Milk Products Co., Ltd.〕	Treatment of phenylketonuria
22	Bropirimine 〔Upjhon Pharmaceuticals Limited, Yakulut Honsha Co., Ltd.〕	Bladder carcinoma in situ
23	Beraprost sodium 〔Toray Industries, Inc.〕	Primary pulmonary hypertension, pulmonary hypertension associated with collagen disease
24	Mycophenolate mofetil 〔Nippon Syntex〕	Treatment of refractory kidney transplant rejection
25	Fludarabine phosphate 〔Nihon Schering K.K.〕	Chronic lymphocytic leukemia accompanied with anemia or thrombocytopenia

The orphan drugs designated in 1995

No.	Name(Name of Manufacturer)	Expected indications or effects
1	(3S)-tetrahydro-3-furyl N-[(1S,2R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl] carbamate monomethanesulfonate (Kissei Pharmaceutical Co., Ltd.)	Treatment of acquired immune deficiency syndrome, antiviral chemotherapy for symptomatic and asymptomatic HIV infection disease
2	Interferon-beta (Toray Industries, Inc.)	Senile disciform macula degeneration with subfoveal and/or juxtafoveal choroidal neovascularization
3	Etidronate disodium (Sumitomo Pharmaceuticals Co., Ltd.)	OPLL : ossification of posterior longitudinal ligament of the spine
4	Cladribine (Janssen-Kyowa Co., Ltd.)	Hairy cell leukemia
5	Anti-human CDlla mouse monoclonal antibody (Pasteur Merieux Serums & Vacciness K.K.)	Inhibition of graft rejection and of graft-versus-host disease (GVHD) in HLA-incompatible bone marrow transplantation in parients suffering from severe combined immunodeficiencies
6	(R)-N-tert-butyl-3-[(2S,3S)-2-hydroxy-3-N-[(R)-2-N-(isoquinolin-5-yloxyacetyl) amino-3-metylthio propanoyl] amino-4-phenylbutanoyl] -1, 3-thiazolidine-4-carboxamide (Japan Energy Corporation)	・ Acquired Immunodeficiency Syndrome (AIDS) ・ Symptomatic and asymptomatic HIV infectious disease less than 400/㎣ CD4 lymphocytes before treatment
7	Cyclophosphamide (Shionogi & Co., Ltd.)	Conditioning regimen for bone marrow transplantation in the treatment of acute leukemia, chronic myelogenous leukemia, myelodysplastic syndrome, malignant lymphoma, multiple myeloma and aplastic anemia
8	Stavudine (Bristol-Myers Squibb K. K.)	Treatment of acquired immune deficiency syndrome, antiviral chemotherapy for symptomatic and asymptomatic HIV infection disease
9	Somatropin (genetical recombination) (Serono Japan Co., Ltd.)	Maintenance or increase of fat free mass in Aquired Immunodeficiency Syndrome (AIDS)
10	Foscarnet sodium hydrate (Aatra Japan Ltd.)	Cytomegalovirus retinitis in patients with AIDS
11	Mesna (Shionogi & Co., Ltd.)	Prevention of urinary disorders (e.g. hemorrhagic cystitis, dysuria) associated with cyclophosphamide administration (used as a conditioning regimen for bone marrow transplantation)

The orphan devices designated in 1995

No.	Name(Name of Manufacturer)	Expected indications or effects
1	Magnetic Cell Separation System (Baxter Ltd.)	Stem cell (CD34 positive cell) selection for allo or auto bone marrow transplantation or auto peripheral blood stem cell transplantation
2	Lymphocyte Depletion Device (Asahi Medical Co., Ltd.)	T-lymphocyte depletion for allogeneic bone marrow transplantation

If you have any questions on Systems for Promotions of Orphan Drug Development, Please contact:

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